The Question of Dosage and Method of Administration of Cardiac Glycosides in Cases of Cardiac Failure

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CARDIAC glycosides are still the most important drugs for the treatment of cardiac failure. In the past, complete digitalization was performed initially (the so-called "saturation method") and then a maintenance dose was administered. For example, digitoxin of more than 0.3 mg per day was given for a few days and 0.1–0.2 mg was given for long term treatment. However, many cases of digitalis intoxication resulted. Recently, the dosage of digitalis has been decreased gradually, but it has been difficult to confirm the efficacy of minor doses of cardiac glycosides. In this panel discussion, the recent dosage and administration method of cardiac glycosides will be discussed. Information

on this problem has been obtained through a questionnaire (Table I) sent to cardiologists at 40 university hospitals and 2 hospitals. (Table II)

(1) Dosage of cardiac glycosides in cases of moderate and severe cardiac failure (NYHA-III and IV) – Tables III and IV.

1. Initial treatment

a. Cardiac Glycosides

Intravenous injection

Deslanoside (Cedilanide or digilanogen C) was used at 33 hospitals (Deslanoside only-23 hospitals) and the initial injection ranged from 0.2 mg to 0.8 mg, with 0.4 mg the most frequently injected dosage. Digoxin was given at 19 hospitals

TABLE I THE QUESTIONNAIRE

(1) Treatment in cases of moderate and severe cardiac failure (NYHA III and IV)		
1. Initial treatment		
a. Cardiac glycosides	Name of drug	Dosage and frequency
Injection		
Oral administration		
b. Diuretics	Name of drug	Dosage and frequency
c. Catecholamine	Name of drug	Dosage and frequency
2. Long term treatment (Maintenance dosage)		
a. Cardiac glycoside	Name of drug	Dosage and frequency
b. Diuretics	Name of drug	Dosage and frequency
(2) Treatment in cases of mild stage of cardiac failure (NYHA II)		
1. Initial treatment		
a. Cardiac glycosides	Name of drug	Dosage and frequency
2. Long term treatment		
a. Cardiac glycosides	Name of drug	Dosage and frequency
(3) Opinion concerning complete digitalization (the so-called "saturation method")		
(4) Opinion concerning a minor dosage of cardiac glycosides (for example 0.05 mg per day of digitoxin)		
(5) How do you use the measurement of blood level of cardiac glycosides?		
(6) Definition of cardiotonic drugs		
(7) Methods of judging the efficacy of cardiotonic drugs (excluding symptoms)		

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TABLE II HOSPITALS

<i>Hokkaido University (Prof. J. Yasuda)</i>	<i>Aichi Medical School (Prof. T. Watanabe)</i>
<i>Sapporo Medical School (Prof. K. Iimura)</i>	<i>Mie University (Prof. H. Takezawa)</i>
<i>Hirosaki University (Prof. Y. Onodera)</i>	<i>Shiga Medical School (Prof. S. Kawakita)</i>
<i>Iwate Medical School (Prof. M. Kato)</i>	<i>Nara Medical School (Prof. H. Ishikawa)</i>
<i>Yamagata University (Prof. S. Yasui)</i>	<i>Kyoto University (Prof. C. Kawai)</i>
<i>Jichi Medical School (Prof. S. Hosoda)</i>	<i>Kyoto Pref. Medical School (Prof. H. Ijichi)</i>
<i>Tsukuba University (Prof. I. Ito)</i>	<i>Kinki University (Prof. R. Katori)</i>
<i>Defence Medical School (Prof. Hosono)</i>	<i>Osaka Medical School (Prof. K. Kawamura)</i>
<i>Chiba University (Prof. Y. Inagaki)</i>	<i>Kobe University (Prof. T. Fukuzaki)</i>
<i>Teikyo University (Prof. E. Miyashita)</i>	<i>Tottori University (Prof. H. Mashiba)</i>
<i>Nippon Medical School (Prof. K. Hayakawa)</i>	<i>Okayama University (Prof. S. Haraoka)</i>
<i>Tokyo University (Prof. T. Sugimoto)</i>	<i>Yamaguchi University (Prof. R. Kusakawa)</i>
<i>Jikei Medical School (Prof. S. Yoshimura)</i>	<i>Tokushima University (Prof. H. Mori)</i>
<i>Toho University (Prof. K. Seki)</i>	<i>Sangyo Medical School (Prof. A. Kuroiwa)</i>
<i>Showa University (Prof. K. Harumi)</i>	<i>Kyushu University (Prof. M. Nakamura)</i>
<i>Kitasato University (Prof. R. Kikawada)</i>	<i>Kyushu University (Prof. H. Yanaga)</i>
<i>Yamanashi Medical School (Prof. K. Tamura)</i>	<i>Nagasaki University (Prof. K. Hashiba)</i>
<i>Kanazawa Medical School (Prof. E. Murakami)</i>	<i>Kurume University (Prof. H. Toshima)</i>
<i>Gifu University (Prof. S. Hirakawa)</i>	<i>Kagoshima University (Prof. H. Tanaka)</i>
<i>Fujita Gakuen University (Prof. Y. Mizuno)</i>	<i>Heart & Vessels Instit. (Dr. K. Kato)</i>
<i>Nagoya City University (Prof. R. Fujinami)</i>	<i>Cent. Adult Diseases Osaka (Dr. S. Toyama)</i>

TABLE III

(1) Treatment in cases of moderate and severe cardiac failure (NYHA III and IV)			
1. Initial treatment			
a. Cardiac glycosides			
Injection	<i>Deslanoside</i>	32 Hospitals	0.2 — 0.4 — 0.8 mg
	<i>Digoxin</i>	19	0.125 — 0.25 — 0.5 mg
Oral adm.	<i>Digoxin</i>	31	0.25 — 0.75 mg
	<i>Digitoxin</i>	13	0.05 — 0.4 mg
	<i>Methyldigoxin</i>	14	0.1 — 0.4 mg
	<i>Lanatoside</i>	1	0.75 mg
	No use	5	
b. Diuretics			
	<i>Furosemida</i>	42	
c. Catecholamine			
	<i>Dopamine</i>	39	
	<i>Dobutamine</i>	39	
2. Long term treatment			
a. Cardiac glycosides			
	<i>Digoxin</i>	37	0.125 — 0.5 mg
	<i>Digitoxin</i>	17	0.025 — 0.15 mg
	<i>Methyldigoxin</i>	14	0.05 — 0.2 mg

(Digoxin only — 10 hospitals). The dosage of digoxin ranged from 0.125 mg to 0.5 mg, with 0.25 mg the most frequently administered dosage.

The subsequent injected was not uniform.
Oral administration
Cardiologists at 5 hospitals did not give

TABLE IV

	Moderate and severe stages		Mild stage	
	Long term treatment	Initial treatment	Long term treatment	
<i>Digoxin</i>	37	34	34	
0.125 mg	19 (51.4%)	11 (32.4%)	23 (67.6%)	
0.25 mg	36 (97.3%)	32 (94.1%)	27 (79.4%)	
0.375 mg	17 (45.9%)	9 (26.5%)	8 (23.5%)	
0.5 mg	5 (13.5%)	4 (11.8%)	2 (5.9%)	
changeable	1 (2.7%)	2 (5.9%)	2 (5.9%)	
<i>Dogotpxom</i>	17	12	13	
0.025 mg	2 (11.8%)	1 (8.3%)	2 (15.4%)	
0.05 mg	10 (58.8%)	7 (58.3%)	10 (76.9%)	
0.075 mg	12 (70.6%)	6 (50.0%)	9 (69.2%)	
0.10 mg	15 (88.2%)	9 (75.0%)	10 (76.9%)	
0.12 mg	4 (23.5%)	3 (25.0%)	2 (15.4%)	
0.15 mg	1 (5.9%)	1 (8.3%)	0	
0.20 mg	0	1	0	
<i>Methyldigoxin</i>	14	13	12	

TABLE V

(2) Treatment in cases of mild cardiac failure (NYHA II)			
1. Initial treatment			
a. Cardiac glycosides			
no use	2 Hospitals		
atrial fibrillation	2		
2. Long term treatment			
Digoxin	34	0.125 – 0.5 mg	
Digitoxin	13	0.025 – 0.12 mg	
Methyldigoxin	12	0.05 – 0.2 mg	
(3) Complete digitalization (the so-called "saturation method")			
fundamentally necessary	5		
severe congestive cardiac failure	6		
not always necessary	15		
not necessary	13		

cardiac glycosides orally for initial treatment. But digoxin was used at 31 hospitals (Digoxin only – 19 hospitals) and the range of dosage was from 0.25 mg to 0.75 mg per day. Digitoxin was administered at 13 hospitals (Digitoxin only – no hospitals) with the dosage ranging from 0.05–0.4 mg per day. Methyldigoxin was given at 14 hospitals (Methyldigoxin only – 2 hospitals) and the range of dosage was from 0.1 mg to 0.4 mg per day. Cardiologists at one hospital used lanatoside 0.75 mg daily.

b. Diuretics

Cardiologists at all 42 hospitals used furose-mide for congestive cardiac failure.

c. Catecholamine

Dopamine and dubutamine were used at 37 hospitals in patients with severe cardiac failure.

2. The maintenance dosage

a. Cardiac glycosides

Oral administration

Digoxin was used at 37 of 42 hospitals and daily dosages ranged from 0.125 mg to 0.5 mg. As shown in Table IV, 0.125 mg was administer-

TABLE VI

(4) Minor dosage of cardiac glycosides	
effective	9
consider as effective	6
effective for elderly patients, kidney disease or hepatic disorders	15
with reference to blood level	3
no use	5
(5) Measurement of blood level of cardiac glycosides	
for prevention, confirmation of intoxication	33
to check effectiveness	7
to determine daily adequate dosage	5
to confirm administration	4
no use	4
for reference	4

TABLE VII

(6) Definition of cardiotonic drugs	
Drugs with positive inotropic action	38
(Increase of cardiac contraction)	
Incidental condition	
improvement of cardiac function or cardiac failure	(9)
no increase of heart rate	(1)
Drug with cardiotonic effect	1
Drug which increase of Vmax	1
Drug which improves of cardiac pump function	1
(7) Method of judging the efficacy of cardiotonic drugs	
hemodynamics	32
echocardiogram	26
CTR (X-ray)	23
exercise tolerance test	8
RI	5
mechanocardiogram	5
Holter ECG	2

ed at 19 hospitals, 0.25 mg at 36 hospitals, 0.375 mg at 17 hospitals and 0.5 mg at 5 hospitals. (When 0.125 mg and 0.25 mg digoxin were given at one hospital, one point was entered at 0.125 mg and one at 0.25 mg in Table IV) Digitoxin was administered at 17 hospitals and the range of daily dosage was from 0.025 mg to 0.15 mg (0.025 mg at 2 hospitals, 0.05 mg including 0.06 mg at 10 hospitals, 0.075 mg including 0.08 mg at 12 hospitals and 0.10 mg at 15 hospitals). Methyldigoxin was given at dosages ranging from 0.05–0.2 mg at 14 hospitals.

The most commonly used daily maintenance dosage of digoxin was 0.25 mg and that of

digitoxin was from 0.05 mg to 0.1 mg. It is interesting to note that 0.025 mg digitoxin was used at 2 hospitals, although in the past it was considered that such a dosage was not effective.

(2) Dosage of cardiac glycosides in cases of mild cardiac failure (NYHA II) Tables IV and V

1. Initial dosage

a. Cardiac glycosides

Cardiac glycosides were not given at 2 hospitals and doctors at 2 hospitals used them only in cases of atrial fibrillation with tachycardia. However, digoxin was administered at 34 hospitals in initial dosages ranging from 0.125 mg to 0.5 mg

(0.125 mg at 11 hospitals, 0.25 mg at 32 hospitals, 0.365 mg at 9 hospitals and 0.5 mg at 5 hospitals). Digitoxin was used at only 12 hospitals and the range of daily dosages was from 0.025 to 0.2 mg (0.025 mg at one hospital, 0.5 mg at 7 hospitals, 0.075 mg at 6 hospitals, 0.1 mg at 9 hospitals, 0.12 mg at 3 hospitals, 0.15 mg at one hospital and 0.2 mg at one hospital). Methyl-digoxin was given at 13 hospitals and the dosage range was from 0.05 mg to 0.2 mg.

2. Maintenance dosage

a. Cardiac glycosides

There was no difference between the dosages for initial treatment and the maintenance dosages. Digoxin was used at 34 hospitals (0.125–0.5 mg per day) and digitoxin was given at 13 hospitals (0.025–0.12 mg per day). Methyl-digoxin was administered at 12 hospitals (0.05–0.2 mg per day). The daily dosage of digoxin was 0.125 mg at 23 hospitals, 0.25 mg at 27 hospitals, 0.365 mg at 8 hospitals and 0.5 mg at 2 hospitals. The dosage of digitoxin was 0.025 mg at 2 hospitals, 0.05 mg at 10 hospitals, 0.075 mg at 9 hospitals, 0.1 mg at 10 hospitals and 0.12 mg at 2 hospitals.

The daily dosage of cardiac glycosides in cases of mild cardiac failure was usually 0.25 mg digoxin, but that of digitoxin was not constant, ranging from 0.05 mg to 0.1 mg; cardiologists at 2 hospitals administered 0.025 mg per day digitoxin.

The questionnaire indicated that the minimum daily dosage was 0.025 mg digitoxin and 0.125 mg digoxin; 0.05 mg digitoxin was used at 13 hospitals and 0.0125 mg digoxin at 23 hospitals. That is minor dosages of digitoxin and digoxin were given at many hospitals.

(3) Opinions of complete digitalization

Complete digitalization or acute digitalization (the so-called "saturation method") was the fundamental method of treatment for cardiac failure. In one cardiology textbook in Japan, the oral dosage of digitalization was given as 1.25–1.5 mg and the maintenance dosage was 0.25–0.5 mg per day. Digitoxin dosage was 0.7–1.2 mg and the maintenance dosage was 0.1 mg. The questionnaire asked cardiologists whether or not they approved of such a method.

Cardiologists at 5 hospitals felt that complete digitalization was necessary fundamentally and it was used in cases with severe congestive cardiac failure at 6 hospitals. However, 15 hospitals felt that such a method was not always necessary and

it was considered not desirable at 13 hospitals. Many doctors did not support the saturation method.

(4) Approval or disapproval of minor dosages of cardiac glycosides for treatment of cardiac failure – Table VI

In this questionnaire, a minor dosage was listed as 0.05 mg per day digitoxin. Cardiologists at 9 hospitals affirmed the effectiveness of minor dosages of cardiac glycosides and those at 6 hospitals, doctors used minor dosages only in elderly patients or those with kidney disease or hepatic disorders. At 3 hospitals, cardiologists used a minor dosage with reference to serum concentration of cardiac glycosides. Doctors at 5 hospitals did not use such a minor dosage.

This result indicates that minor dosages of cardiac glycosides were approved by doctors at 15 hospitals. Cardiologists at 15 hospitals limited their use of minor dosages.

(5) The measurement of blood level of cardiac glycosides

The blood level of cardiac glycosides was measured at many hospitals. Cardiologists at 33 hospitals used the measurement for prevention or confirmation of intoxication of glycosides. It was used to check the effectiveness of cardiac glycosides at 7 hospitals and for determining the daily adequate dosage at 5 hospitals. At 4 hospitals, the blood level was measured to confirm the administration of cardiac glycosides and at 4 hospitals it was not used. At 4 hospitals, doctors answered that method was used for reference.

(6) Definition of cardiotonic drugs – Table VII

Many new positive inotropic agents have been developed and it is necessary to determine a definition for cardiotonic drugs. Cardiotonic drugs were defined as drugs with positive inotropic action or which increased cardiac contraction by doctors at 38 hospitals. Cardiologists at 9 hospitals added the incidental condition of improving cardiac function on cardiac failure; one doctor answered that no increase of heart rate was necessary. One doctor defined the drug as having a cardiotonic effect, one that it increased V_{max} and one defined it as a drug which improved cardiac pump function.

(7) Method of judging the efficacy of cardiotonic drugs – Table VII

It is important to determine a method for

judging the effectiveness of cardiotonic drugs, because many new positive inotropic agents have been used. In the past, judgements of efficacy were based on symptoms and chest X-rays. It is important that the drugs be objectively. In the questionnaire, objective methods used were

hemodynamics at 32 hospitals, echocardiogram at 26 hospitals, CTR of X-ray at 23 hospitals, exercise tolerance test at 8 hospitals and radio-isotope technique at 5 hospitals.

We express our thanks to cardiologist at 42 hospitals who answered the questionnaire.